

BEST AVAILABLE COPY

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
31 January 2002 (31.01.2002)

PCT

(10) International Publication Number
WO 02/07870 A2(51) International Patent Classification⁷: B01J

(21) International Application Number: PCT/US01/22128

(22) International Filing Date: 13 July 2001 (13.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/625,216 24 July 2000 (24.07.2000) US(71) Applicant: CHEVRON U.S.A. INC. [US/US]; 2613
Camino Ramon, 3rd Floor, San Ramon, CA 94583-4289
(US).(72) Inventors: O'REAR, Dennis, J.; 40 Upland Drive,
Petaluma, CA 94952 (US). KIBBY, Charles, L.; 846
Clifton Ct., Benicia, CA 94510 (US). SCHEUERMAN,
Georgianna, L.; 1155 Sanders Drive, Moraga, CA 94556
(US).(74) Agent: AMBROSIUS, James, W.; Chevron Corporation,
Law Department, Post Office Box 6006, San Ramon, CA
94583-0806 (US).(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished
upon receipt of that reportFor two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: USE OF COMBINATORIAL CHEMISTRY TO OPTIMIZE MULTI-STEP SYNTHESIS

(57) Abstract: Methods for discovering optimum catalysts and/or reaction conditions for performing multi-step reactions, in particular multi-step catalytic reactions, are disclosed. A combinatorial approach is used to identify optimum catalysts and/or reaction conditions for performing the reactions. The reactions are performed in the voids of a suitable reactor capable of handling conditions of elevated temperature and pressure, and also that can handle a plurality of simultaneous or substantially simultaneous reactions. The methods can advantageously be used to generate a database of combinations of catalyst systems and/or reaction conditions that provide various product streams, such that as market conditions vary and/or product requirements change, conditions suitable for forming desired products can be identified with little or no downtime. The catalysts can be evaluate using varied reaction conditions, which can provide a) a combinatorial library of product streams and a database including the combination of catalysts and reaction conditions to provide each product stream and/or b) the optimum combination of catalysts and reaction conditions for obtaining a desired product stream.

WO 02/07870 A2

WO 02/07870

PCT/US01/22128

Use of Combinatorial Chemistry to Optimize Multi-Step Synthesis

Field of the Invention

This invention is generally in the area of combinatorial chemistry, in particular the
5 use of combinatorial chemistry to optimize multi-step synthesis.

Background of the Invention

Combinatorial chemistry is in widespread use in the pharmaceutical industry, where
it is used to synthesize, purify and evaluate new drugs at a tremendously fast pace. The
10 reactions are typically performed at a relatively small scale, since only a small amount of
each drug is required for testing. Typically, only those drugs that are active in relevant
bioassays are produced in larger quantities. The type of chemistry used to generate
commercial quantities of the drugs is rarely the same as that used in small scale synthesis.
The syntheses typically involve taking a core molecule with one or two sites for covalent
15 attachment of various moieties, and attaching a plurality of different moieties to these sites,
often in a single step. The chemistry is typically not optimized because the goal is to find an
optimum compound rather than an optimum method for making the compound.

Combinatorial chemistry is also being used in petroleum chemistry. Unlike
pharmaceutical chemistry, a major goal in petroleum chemistry is to optimize the reaction
20 conditions and catalysts used for particular reactions rather than to synthesize, purify and
evaluate a plurality of products. Many petroleum products are prepared in multi-step
syntheses. There is a need to develop combinatorial methods that are directed to multi-step
syntheses. The present invention provides such methods.

Summary of the Invention

The present invention is directed to devices and methods for optimizing multi-step
syntheses using combinatorial chemistry. Many of the multi-step reactions require the use
of elevated temperatures and/or pressures, and the devices typically must be able to handle
these conditions and also be useful for conducting a plurality of simultaneous or
30 substantially simultaneous reactions. The plurality of reactions can use individual catalysts
or combinations thereof, such that all or part of a combinatorial library of catalysts can be
evaluated.

WO 02/07870

PCT/US01/22128

In one embodiment, the multi-step syntheses are those in which a single catalyst or combination of catalysts performs two or more substantially simultaneous steps in a single reaction vessel. Examples of such syntheses include Fischer-Tropsch synthesis where the product is isomerized *in-situ*, and isosynthesis (defined herein as the conversion of syngas to methanol and the subsequent conversion of methanol to higher molecular weight products).
5 Another example is the molecular rearrangement of paraffins, where a dehydrogenation/hydrogenation catalyst converts the paraffins to olefins, a metathesis catalyst metathesizes the olefins, and the dehydrogenation/hydrogenation catalyst then hydrogenates the metathesized olefins. Yet another example involves the *in-situ*
10 dehydrogenation of paraffins to form olefins, and the subsequent alkylation of aromatics with the olefins. Additional examples include catalytic reforming, paraffin isomerization, hydrocracking, hydroisomerization of lube oils, and the like.

In this embodiment, the reactor includes a plurality of voids, and at least a substantial number of the voids include a combination of catalysts, where the catalysts are
15 selected from libraries of catalysts capable of catalyzing the individual steps of the multi-step synthesis. Using the device, a plurality of catalyst combinations can be evaluated simultaneously.

In another embodiment, the multi-step syntheses are those in which a single step is carried out in one reaction vessel and a second step is carried out in a separate reaction
20 vessel, optionally with a purification step between the reaction steps. One such synthesis involves the hydrocracking of wax to form low molecular weight olefins, and the subsequent oligomerization of those olefins. Another example involves the oligomerization of olefins and subsequent isomerization of the olefins to form a desired product stream. A multi-step reaction can be performed in a single reactor, and the product stream subjected to
25 one or more additional steps in a second reactor.

In either embodiment, the catalyst libraries can be prepared by taking a single catalyst and subjecting it to a number of systematic additions or modifications to the catalyst to form a second library. For example, a zeolite could be modified by impregnating or exchanging different metals or levels of metals to form a second library. The zeolite
30 function and the metal function can each be used to satisfy different catalyst requirements for different steps in the multi-step synthesis, and a single library with catalysts exhibiting both activities can be generated.

WO 02/07870

PCT/US01/22128

Although the methods are generally applicable to multi-step synthesis, they are particularly applicable to petroleum chemistry. Virtually all petroleum products are prepared via multi-step synthesis, and the combinatorial methods described herein permit optimization of virtually all of these syntheses by selecting appropriate catalysts, reactants and reaction conditions. The products can include olefins such as ethylene, normal and iso-paraffins, aromatics and combinations thereof, and preferably include iso-paraffins in the distillate fuel and/or lube base stock ranges, and more preferably, iso-paraffins in the jet or diesel range. The methods use a combinatorial approach to identify optimum reaction conditions and catalysts or catalyst combinations for performing the desired multi-step syntheses. The methods involve obtaining an appropriate device that includes a plurality of voids for conducting the reactions, which device is capable of handling elevated temperatures and pressures, placing an effective amount of a catalyst (or a catalyst combination) from one or more catalyst libraries in a void, repeating this step as necessary with different voids and different catalysts, and performing the desired reactions.

Preferably, the preparation of the catalyst libraries and/or the transfer of the catalysts to the reaction vessels is automated. The product streams are preferably analyzed, for example by GC, HPLC and/or GC/MS. Preferably, the analytical techniques are set up to handle a plurality of simultaneous analyses or otherwise optimized to handle the plurality of samples.

The reaction conditions, catalysts and analytical information regarding the product streams are preferably stored in a database.

The methods can advantageously be used to generate a database of catalysts and, optionally, reaction conditions, which provide various product streams. As market conditions vary and/or product requirements change, conditions suitable for forming desired products can be identified with little or no downtime using the methods described herein.

Detailed Description of the Invention

The present invention is directed to devices and methods for optimizing multi-step syntheses using combinatorial chemistry. In one embodiment, the multi-step syntheses are those in which a single catalyst or combination of catalysts performs two or more substantially simultaneous steps in a single reaction vessel. In another embodiment, the multi-step syntheses are those in which a single step is carried out in one reaction vessel,

WO 02/07870

PCT/US01/22128

and a second step is carried out in a separate reaction vessel, optionally with a purification step between the reaction steps. A multi-step reaction can be carried out in a single reaction vessel, and the product stream sent to a second reaction vessel for one or more additional process steps.

5 Virtually all petroleum chemistry involves multi-step synthesis, and the combinatorial methods described herein permit optimization of virtually all of these syntheses using appropriate catalysts, reactants and reaction conditions. The methods use a combinatorial approach to identify optimum reaction conditions and catalysts or catalyst combinations for performing the desired multi-step syntheses. The methods involve
10 obtaining an appropriate device that includes a plurality of voids for conducting the reactions, which device is capable of handling elevated temperatures and pressures, placing an effective amount of a catalyst (or a catalyst combination) from one or more catalyst libraries in a void, repeating this step as necessary with different voids and different catalysts, and performing the desired reactions. The product streams are preferably
15 analyzed, for example by GC, HPLC and/or GC/MS. The reaction conditions, catalysts, and analytical information regarding the product streams are preferably stored in a database.

 The methods can advantageously be used to generate a database of catalysts and, optionally, reaction conditions, which provide various product streams. As market conditions vary and/or product requirements change, conditions suitable for forming desired
20 products can be identified with little or no downtime using the methods described herein.

Types of Reactions

 The devices and methods can be used to evaluate and optimize virtually any type of multi-step reaction. Preferred reactions are catalytic reactions. These types of reactions are
25 well known to those of skill in the art. In one embodiment, the multi-step syntheses are those in which a single catalyst or combination of catalysts performs two or more substantially simultaneous steps in a single reaction vessel.

 Examples of such syntheses include gas-to-liquid reactions, for example Fischer-Tropsch synthesis where an olefinic product is isomerized *in-situ*, and isosynthesis (defined
30 herein as the conversion of syngas to methanol and the subsequent conversion of methanol to higher molecular weight products). Another example is the molecular rearrangement of paraffins, where a dehydrogenation/hydrogenation catalyst converts the paraffins to olefins,

WO 02/07870

PCT/US01/22128

a metathesis catalyst metathesizes the olefins, and the dehydrogenation/hydrogenation then hydrogenates the metathesized olefins. Yet another example involves the *in-situ* dehydrogenation of paraffins to form olefins, and the subsequent alkylation of aromatics with the olefins. Additional examples include catalytic reforming, paraffin isomerization, hydrocracking, hydroisomerization of lube oils, and the like.

In another embodiment, the multi-step syntheses are those in which a single step is carried out in one reaction vessel, and a second step is carried out in a separate reaction vessel, optionally with a purification step between the reaction steps. One such synthesis involves the hydrocracking of wax to form low molecular weight olefins, and the subsequent oligomerization of those olefins. Another synthesis involves the oligomerization of olefins and subsequent isomerization of the olefins to form a desired product stream. Other types of reactions that can be one of the steps in a multi-step synthesis include hydroformylations, ether synthesis, hydrocracking, isode waxing, isomerizations, dehydrogenations, alkylations, dehydrocyclization, catalytic reforming, including rheniforming and platforming, olefin metathesis, dimerization, oligomerization, and polymerization.

In addition to the petroleum chemistry described above, the methods can be applied to other synthetic chemistry as well. Such chemistry can be performed using solid phase or solution phase chemistry.

Examples of reactions that can be done in either solid or solution phase include, for example, condensation reactions for preparing amides, esters, ureas, imines, and phosphorous compounds. Various carbon-carbon bond forming reactions can be performed using solid and solution phase chemistry. Examples include Suzuki reactions, organozinc reactions, Stille coupling reactions, Heck reactions, enolate alkylations, Wittig reactions, Horner-Wadsworth-Emmons reactions, metathesis reactions such as ruthenium-catalyzed metathesis of polymer-bound olefins, Mitsunobu reactions, nucleophilic displacement of support-bound α -bromoamides in the submonomer preparation of peptoids, thiol alkylation, anilide alkylation with primary alkyl halides, one pot cyclization and anilide alkylation in the solid-phase synthesis of 1,4-benzodiazepine-2,5-diones, successive amide alkylations (generating new combinatorial peptide libraries from existing combinatorial peptide libraries), benzophenone imine α -carbon alkylation, alkylation or sulfonylation of a support-bound phenol, enolate monoalkylation, alkylation of support-bound 1,3-diketones in the

WO 02/07870

PCT/US01/22128

solid-phase synthesis of pyrazoles and isoxazoles, tosyl displacement with primary or secondary amines, Gignard reactions, S_NAr reactions, Michael additions, iodoetherification reactions, oxidations, reductions, such as reductive alkylation, Pictet-Spengler reactions, and the like.

5 The types of reactions used will be expected to vary according to the types of catalysts in the libraries as well as the types of substitutions that will be made. Those of skill in the art can readily determine appropriate sets of reactions and reaction conditions.

Reactants

10 When the methods are used to optimize petroleum chemistry, the reactants are typically paraffins, olefins, oxygenates and aromatics. Suitable reactants may be low molecular weight gases, liquids at room temperature, or solids or viscous liquids at room temperature. Examples of reactants that are gases at room temperature include hydrogen gas, carbon monoxide, carbon dioxide, oxygen, and syngas (a mixture of carbon monoxide
15 and hydrogen gas). Examples of reactants that are gases or liquids at room temperature include low molecular weight olefins and/or paraffins (typically including less than 6 carbon atoms), low molecular weight oxygenates such as methanol, ethanol, and dimethyl ether. Examples of reactants that are solids or viscous liquids at room temperature include high molecular weight oils and waxes.

20 When the methods are used to optimize pharmaceutical chemistry and other areas of chemistry, other reactants are typically used, optionally without using catalysts. Those of skill in the art can readily identify appropriate reactants for performing a desired synthesis.

 The reactants can be reacted in any suitable ratio and amount, given the size of the voids in the reaction vessels and the desired conversions. The reactants preferably come
25 from a common source, to ensure consistency between reactions. A splitter can be used, for example to direct the reactants to the plurality of voids.

Products

 When the methods are used to optimize petroleum chemistry, the products are
30 typically hydrocarbons useful as naphtha, distillate fuels, lube oils, waxes, or as components in such products. The products generally are olefins such as ethylene, normal and iso-paraffins, aromatics and combinations thereof, and preferably include iso-paraffins in the

WO 02/07870

PCT/US01/22128

distillate fuel and/or lube base stock ranges, and, more preferably, iso-paraffins in the jet or diesel range. When the methods are used to optimize other chemistry, the products can be virtually any type of organic chemical.

5 Catalysts

Suitable catalysts for performing various reactions, particularly in the field of petroleum chemistry, are well known to those of skill in the art. Catalyst libraries including such catalysts, and combinations thereof, can be readily prepared. Libraries include a plurality of catalysts, preferably at least 10 catalysts, more preferably at least 50 catalysts
10 and most preferably at least 100 catalysts. Large numbers of catalysts can be evaluated, for example by using a plurality of voids in single reactor and/or by performing parallel runs with a plurality of reactors.

The amount of the catalyst(s) used in the reaction depends on the size of the void and the size of the reaction. Those of skill in the art can readily determine an appropriate
15 amount of catalyst for a particular reaction. In many multi-step syntheses, the catalysts are zeolites, other molecular sieves such as borosilicates, ELAPOs such as SAPOs, Fischer-Tropsch catalysts, or noble metals.

Fischer-Tropsch Catalysts

Fischer-Tropsch catalysts contain a Group VIII transition metal on a metal oxide
20 support. The catalysts may also contain a noble metal promoter(s) and/or crystalline molecular sieves. Certain catalysts are known to provide chain growth probabilities that are relatively low to moderate, and the product of the reaction includes a relatively high proportion of low molecular (C_{2-8}) weight olefins and a relatively low proportion of high molecular weight (C_{30+}) waxes. Certain other catalysts are known to provide relatively high
25 chain growth probabilities. Such catalysts are well known to those of skill in the art and can be readily obtained and/or prepared.

Zeolites

Catalysts useful in catalytic multi-step reactions typically include one or more
30 zeolites and/or non-zeolitic molecular sieves. The acidity of the zeolites varies greatly. Depending on the particular type of reaction and desired product composition, the acidity may have a strong effect on the product distribution. Accordingly, in some embodiments, it

WO 02/07870

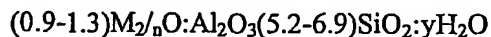
PCT/US01/22128

may be desirable to evaluate a plurality of zeolites with a range of acidities. The same holds true for the other types of catalysts described herein.

Useful zeolites and/or molecular sieves can be small, large and/or intermediate pore size zeolites, all of which can be included in the catalyst libraries. However, in many cases, the art has a reasonable amount of knowledge about which types of zeolites are preferred, and the catalyst libraries can advantageously be limited to such catalysts.

Examples of these catalysts, any and all of which can be included in the catalyst libraries, are described, for example, in U.S. Patent Nos. 3,546,102; 3,574,092; 3,679,575; 4,018,711; 4,104,320; 4,347,394; 4,370,224; 4,417,083; 4,434,311; 4,447,316 and 5,559,068. Zeolite-containing catalysts, for example the zeolite mordenite, ZSM-type zeolites, zeolite L, Faujasites X and Y, and the zeolite omega, are preferably included into the catalyst libraries. L-zeolites and zeolites having an L-zeolite-type channel structure and size, such as ECR-2, which is described in U.S. Patent No. 4,552,731, and ECR-31, which is described in U.S. Patent No. 5,624,657 (Vaughan), are also preferably included in the libraries.

The composition of type L -zeolite expressed in terms of mole ratios of oxides may be represented by the following formula:



In the above, formula M represents a cation, n represents the valence of M, and y may be any value from 0 to about 9. Zeolite L, its X-ray diffraction pattern, its properties, and method for its preparation are described in detail in, for example, U.S. Patent No. 3,216,789, the contents of which is hereby incorporated by reference. The actual formula may vary without changing the crystalline structure. For example, the mole ratio of silicon to aluminum (Si/Al) may vary from 1.0 to 3.5.

Examples of useful large pore zeolites include ZSM-3, ZSM-4, ZSM-10, ZSM-12, ZSM-20, zeolite beta, zeolite omega, zeolite L, zeolite X, zeolite Y, REY, USY, RE-USY, mordenite, LZ-210, LZ-210-M, LZ-210-T, LZ-210-A, SSZ-24, SSZ-26, SSZ-31, SSZ-33, SSZ-35, SSZ-37, SSZ-41, SSZ-42, SSZ-44 and MCM-58, any and all of which are preferably incorporated into the libraries. ZSM-3 is described in U.S. Patent No. 3,415,736. ZSM-4 is described in UK Application No. 1,117,568. ZSM-10 is described in U.S. Patent No. 3,692,470. ZSM-12 is described in U.S. Patent No. 3,832,449. ZSM-20 is described in

WO 02/07870

PCT/US01/22128

U.S. Patent No. 3,972,983. Zeolite beta is described in U.S. Patent No. Re. 28,341 (of original U.S. Patent No. 3,308,069). Zeolite omega is described in U.S. Patent No. 4,241,036. Zeolite L is described in U.S. Patent No. 3,216,789. Zeolite X is described in U.S. Patent No. 2,882,244. Zeolite Y is described in U.S. Patent No. 3,130,007. LZ-210, LZ-210M, LZ-210-T, LZ-210-A and mixtures thereof are described in U.S. Patent No. 4,534,853. SSZ-24 is described in U.S. Patent No. 4,834,977. SSZ-26 is described in U.S. Patent No. 4,910,006. SSZ-31 is described in U.S. Patent No. 5,106,801. SSZ-33 is described in U.S. Patent No. 4,963,337. SSZ-35 is described in U.S. Patent No. 5,316,753. SSZ-37 is described in U.S. Patent No. 5,254,514. SSZ-41 is described in U.S. Patent No. 5,591,421. SSZ-42 is described in U.S. Serial No. 08/199,040. SSZ-44 is described in U.S. Patent No. 5,580,540. MCM-58 is described in U.S. Patent No. 5,437,855.

Examples of useful intermediate pore size zeolites include ZSM-5, ZSM-11, ZSM-22, ZSM-23, ZSM-35; ZSM-48, ZSM-57, SSZ-4, SSZ-23; SSZ-25; SSZ-28, SSZ-32, and SSZ-36. ZSM-5 is described in U.S. Patent No. Re. 29,948 (of original U.S. Patent No. 3,702,886). ZSM-11 is described in U.S. Patent No. 3,709,979. ZSM-22 is described in U.S. Patent No. 4,556,477. ZSM-23 is described in U.S. Patent No. 4,076,842. ZSM-35 is described in U.S. Patent No. 4,016,245. ZSM-48 is described in U.S. Patent No. 4,585,747. SUZ-4 is described in EP Application No. 353,915. SSZ-23 is described in U.S. Patent No. 4,859,422. SSZ-25 is described in U.S. Patent Nos. 4,827,667 and 5,202,014. SSZ-28 is described in U.S. Patent No. 5,200,377. SSZ-32 is described in U.S. Patent No. 5,053,373. The entire contents of all these patents and patent applications are incorporated herein by reference, and any and all of the catalysts described therein can be incorporated into the catalyst libraries.

Catalyst Pre-Treatment

The catalysts may perform substantially differently if subjected to different pre-treatments. Examples of catalyst pre-treatment conditions that can be varied include the time and temperature of catalyst washing, heating rate, hold time, hold temperature, relative humidity during drying or calcining; hydrogen content and total pressure during catalyst reduction, CO partial pressure during activation in CO; treatment with citrate, alcohols, or metal hydrides, modification of catalyst acidity, vapor deposition of Si or Al species, and

WO 02/07870

PCT/US01/22128

steaming. Any or all of these can be performed and modified to increase the size of the catalyst library. Alternatively, where those of skill in the art generally understand which pre-treatments are preferred for a given catalyst, the pre-treatment can be one that is conventionally used in the art. This may be preferred to minimize the size of the catalyst library being evaluated.

Catalyst libraries can be prepared by taking a single catalyst and subjecting it to a number of systematic additions or modifications to the catalyst to form a second library. For example, a zeolite could be modified by impregnating or exchanging different metals or levels of metals to form a second library. The zeolite function and the metal function can each be used to satisfy different catalyst requirements for different steps in the multi-step synthesis, and a single library with catalysts exhibiting both activities can be generated. Accordingly, this approach may be preferred where both steps are performed in a single reactor.

Catalyst Supports

Catalysts used in these reactions may be present on a support. Suitable metal oxide supports or matrices that can be used to minimize methane production include alumina, titania, silica, aluminum phosphate, magnesium oxide, alkaline earth titanates, alkali titanates, rare earth titanates and mixtures thereof. The catalysts can include any or all of these supports, in varying ratios of weight of support to weight of catalyst.

Typically, fluid catalysts have a particle size of between 10 and 110 microns, preferably between 20 and 80 microns, more preferably between 25 and 65 microns, and have a density of between 0.25 and 0.9 g/cc, preferably between 0.3 and 0.75 g/cc. Extrudates or pellets are fine for some reactions and their sizes are typically between 1 and 10 mm.

Logical Arrays

Libraries of catalysts can be prepared and evaluated using the methods described herein. The identity of the catalyst or combination thereof in each position in the voids in the reactors can be stored in a computerized device, or identified via other identifying means. The products of the reaction can be readily identified, for example by gas chromatography (GC), a combination of gas chromatography and mass spectrometry (GC/MS), infrared heat emissions, infrared species analysis, or UV spectral analysis. To

WO 02/07870

PCT/US01/22128

avoid contaminating the columns in chromatographic devices, it may be desirable to filter a representative sample of the product stream before it is placed on the column, for example by backflushing or using an in-line filter or an in-line solid phase extraction (SPE) column.

The properties of the reaction products generated during the evaluation of the libraries for a particular chemical reaction can be measured and correlated to specific catalysts, combinations of catalysts, and/or reaction conditions. By screening numerous combinations of catalysts and/or reaction conditions, the selection of the optimal combinations is more a function of the data collection method than the "rational" basis for selecting a useful catalyst and/or set of reaction conditions.

There are several types of reactions in which two or more types of catalysts are used. These catalyst combinations may be used simultaneously or in series, for example in multi-step syntheses. Combinations of catalysts may be used, for example, in multi-step reactions, where one catalyst performs one step, and a second catalyst performs a second step.

Examples of such reactions include isosynthesis and Fischer-Tropsch synthesis where an acidic catalyst is used to isomerize the olefins as they are formed. In such reactions, the optimum overall catalyst combination for producing a desired product may not be the one that includes the optimum catalyst for both steps, since both steps may require totally different reaction conditions to be optimized. The overall optimum combination may be one that is the optimum for the first step or for the second step or a compromise between the two steps.

For example, the optimum conditions for Fischer-Tropsch synthesis may involve temperatures at a first temperature range, but the optimum olefin isomerization catalysts may operate best at temperatures at a different temperature range. When these "optimum" olefin isomerization catalysts are operated at temperatures in the first temperature range, they may be inefficient. Accordingly, it is preferred that the catalyst combinations include a combination that is optimum for all steps in the multi-step reaction. It is therefore important to test both catalyst components together. However, leads for this screening of optimum catalyst combinations can come from searching the individual catalysts.

When catalyst combinations are used, the catalysts are preferably combined in a logical manner, for example in an A x B array, where each position in the A column includes one or more catalysts for performing the first step of the reaction, and each position in the B row includes one or more catalysts for performing the second step of the reaction.

WO 02/07870

PCT/US01/22128

In this manner, virtually every possible combination of catalysts in the libraries can be evaluated. It may be important for some reactions that a particular catalyst be upstream from another. For other reactions, for example, those where intermediates from one catalyst are converted to final products on the second catalyst, an intimate mixture of the two catalysts may be preferred. Typical particle sizes for these types of catalyst mixtures are in the micron range.

The combinations of catalysts can be evaluated using varied reaction conditions, which can provide a) a combinatorial library of product streams and a database including the combination of catalysts and reaction conditions to provide each product stream and/or b) the optimum combination of catalysts and reaction conditions for obtaining a desired product stream.

Reaction Conditions

The reaction conditions typically involve increased temperature and pressure. Typical pressure ranges are from 0.1 to 500 ATM, preferably from 1 to 50 ATM, more preferably from 1 to 25 ATM. Typical temperature ranges are from 20 to 1300°F, preferably from 100 to 1000°F, more preferably from 200 to 750°F. Flow rates through the reactor would be expected to vary depending on the size of the voids in the reactor and the type of chemistry being performed. Those of skill in the art can readily optimize the flow rates through the reaction vessels. These conditions may be but need not be the same as those used in large scale commercial reactors. Additional reaction conditions that can be modified are those in which the catalysts are pre-treated. Pre-treatment steps for various catalysts are well known to those of skill in the art and are described elsewhere herein.

Preferably, the absolute pressure is not more than 50%, more preferably 35%, most preferably, 20% higher or lower than would be used in a commercial plant. The temperature is preferably not more than 200°F, more preferably not more than 100°F, and most preferably, not more than 50°F higher or lower than would be used commercially. Preferably, the flow of reagents follows the same path (i.e., downflow, upflow, mixed reactor) as they would in a commercial plant. Preferably, the reagents are in the same phases as would be used commercially.

WO 02/07870

PCT/US01/22128

Reactors

As used herein, a reaction vessel is any suitable container that can hold a plurality of combinations of catalyst systems, that can preferably contain from about 200 mg to about 100 g, more preferably from about 1 mg to about 10 g of each catalyst combination, and that
5 can handle the reaction conditions necessary for converting syngas to product streams including hydrocarbons in the distillate fuel and/or lube base oil ranges, for example conditions of increased pressure and temperature.

Any reaction vessel that is capable of being used to conduct a plurality of simultaneous reactions using gas phase reactants and solid catalysts under conditions of
10 elevated temperature and pressure can be used. Such reaction vessels are well known to those of skill in the art. Examples of suitable devices include those described, for example, in U.S. Patent No. 5,980,839 to Bier et al., U.S. Patent No. 6,036,923 to Laugharn, Jr. et al., U.S. Patent No. 6,030,917 to Weinberg et al., U.S. Patent No. 6,001,311 to Brennan, the contents of each of which are hereby incorporated by reference.

15 The reaction vessel can contain multiple sample vessels, in parallel or in series, to perform combinatorial or sequential operations, respectively. The reactor can include a reaction region that includes a plurality of individual reaction cavities or voids, each of which can have a port adapted to supply or remove reagents, solvents, gases and/or vacuum suction to the void.

20 Preferably, the reactors include ten or more voids, more preferably greater than 25 voids, most preferably greater than 50 voids. The size of the voids is typically between about 0.1 and 10 ml, preferably between about 1 and 2 ml, and more.

The voids are an appropriate size for receiving the catalysts used for the reactions and for permitting the entry and exit of reactants and products. The reactors can be prepared
25 from any suitable material, including metals and alloys, polymers, plastics, glass, ceramics, semi-conductors, and the like. They can be formed from a solid material, or can be in the form of laminates. The materials must be able to withstand the reaction conditions and also be inert to the catalysts and reactants employed.

Some or all of the voids are used to carry out the desired multi-step reactions. The
30 individual voids include individual catalysts or combinations thereof, such that all or part of a combinatorial library of catalysts can be evaluated. The devices can also include channels that are used to provide heating and cooling, or heating and cooling can be provided using

WO 02/07870

PCT/US01/22128

other means. For example, the reactor can be heated and/or cooled externally and thus heat and/or cool the reactions occurring in the various voids.

Preferably, the reactants are fed to the voids from a single source, for example using a splitter or other suitable means to pass the reactants at approximately the same flow rate to the voids in which the reactions are to occur. There can be a mixing region disposed adjacent to the reaction region, such that the reaction voids open into the mixing region.

The scale of the synthetic reactions is preferably in the range of greater than about 200 mg, more preferably between one mg and 100 g, although the scale can be modified depending on the amount of compound necessary for the particular application. The reactions may be performed under conditions of relatively high temperature and/or pressure. Following the reactions, the products can be characterized using a variety of means, for example GC, GC/MS, HPLC and the like.

Robotic arms and multi-pipet devices can be used to add appropriate catalysts to the appropriate locations in the reaction vessel. When appropriate, the chemistry can be performed under varying conditions of temperature, pressure, flow rate and the like. When elevated temperatures and pressures are required, devices capable of handling elevated temperatures and pressures, particularly for use in combinatorial chemistry, are used.

In one embodiment, the reactions are carried out via computer control. The identity of each of the catalysts can be stored in a computer in a "memory map" or other means for correlating the data regarding the chemical reactions to the catalyst combinations in the reaction vessels. Alternatively, the chemistry can be performed manually and the information stored, for example on a computer.

Those of skill in the art can readily determine appropriate sets of reactions and reaction conditions to generate and/or evaluate the libraries of interest.

Analytical Equipment

The products from the reactions are preferably analyzed after the reactions are complete. Suitable analytical equipment for analyzing the products of chemical reactions, particularly reactions common to petroleum chemistry, are well known to those of skill in the art.

After the chemical reactions take place, the reaction products can be individually transferred from the individual voids to an analytical device. Any device that can take

WO 02/07870

PCT/US01/22128

samples from the individual voids in the reactors and analyze the resulting compounds can be used.

The analytical device is a preferably chromatographic device, such as an analytical or preparative scale HPLC, GC or GC/MS, although other devices can be envisioned, depending on the chemistry performed. The devices are preferably optimized for high-speed analysis, for example, by using short, directly heated separation columns, to more effectively handle the large number of samples. Since the product streams may not include UV-active compounds, the analytical equipment preferably includes an ELSD detector or other detector that is not dependent on UV absorption to detect a compound eluting from the column.

Particularly when iso-paraffin concentration is evaluated using the library, a combination of GC and MS is used. Isomers tend to have the same MS peaks, but elute at different times from the columns, and this technique allows rapid determination of the product stream.

The products can be assayed for various properties, including octane and/or cetane values, degree of isomerization, olefin concentration, and the like. Preferably, the products are analyzed in a high-throughput manner. Conditions are known in the art for determining the octane or cetane values based on known GC data, when a GC is performed on a representative sample of the product stream. These techniques may be particularly useful in evaluating the libraries for useful catalyst combinations for preparing products with desirable properties.

Using information obtained in the analyses, those of skill in the art can readily optimize the reactions by varying various process conditions, for example reagent composition, temperature, pressure, flow rate and the like.

Database

Data regarding the catalysts or combinations thereof, reaction conditions and product streams can be stored in a relational database. The database can be used to find optimum catalyst combinations for producing a desired product stream, and can be particularly useful when the desired product stream varies depending on market factors. When the product requirements change, appropriate catalysts and/or reaction conditions can be selected to prepare the desired product.

WO 02/07870

PCT/US01/22128

The data is preferably stored in a computer system capable of storing information regarding the identity of the catalysts and the product streams obtained, particularly when a plurality of different reaction conditions are used. Software for managing the data is stored on the computer. Relational database software can be used to correlate the identity of the ionic liquids, the reaction conditions (for example reagent composition, temperature and pressure) and the analytical data from each product stream. Numerous commercially available relational database software programs are available, for example from Oracle, Tripos, MDL, Oxford Molecular ("Chemical Design"), IDBS ("Activity Base"), and other software vendors.

Relational database software is a preferred type of software for managing the data obtained during the processes described herein. However, any software that is able to create a "memory map" of the catalysts in the reaction vessels and correlate that information with the information obtained from the chemical reactions can be used. This type of software is well known to those of skill in the art.

Library Design

Software for the design of test libraries can be used to design the original catalyst test libraries based on input from literature and previous experimental programs. This software can be used to efficiently design test libraries that cover the desired experimental space and utilize statistical experimental design methods.

Other software can be used to analyze the data from experiments and correlate that data with the structure of the catalysts and/or catalyst treatment conditions and/or reaction conditions. Such correlations are often referred to as QSAR software (Quantitative Structure Activity Relations). Such QSAR can then be used by the software to design subsequent catalyst test libraries for further screening. The use of such QSAR programs can add to the efficiency of screening. As more data is collected, these QSAR programs can become more efficient at developing catalyst libraries with increased probability for finding desirable catalysts.

Methods

The methods use a combinatorial approach to identify optimum reaction conditions and catalysts or catalyst combinations for performing the desired reactions and/or for providing a desired product. In one embodiment, the reaction conditions (reactant

WO 02/07870

PCT/US01/22128

composition, temperature and pressure) are kept reasonably constant while evaluating the entire library, and then the reaction conditions are modified and the library is re-evaluated with the modified reaction conditions. In another embodiment all of the significant variables are varied at once. In either embodiment it may be easier and faster
5 experimentally to give all catalysts a common pre-treatment, modifying the pre-treatments as desired to increase the size of the catalyst library.

Where the multi-step synthesis involves performing all of the steps in a single reactor at substantially the same time, the steps involve obtaining a suitable reactor that includes a plurality of voids, placing an effective amount of a catalyst (or a catalyst
10 combination) from one or more catalyst libraries in a void, repeating this step as necessary with different voids and different catalysts so that a plurality of catalysts can be simultaneously evaluated, and performing the desired reactions. The product streams are then preferably analyzed, more preferably by GC, HPLC or GC/MS. The reaction conditions, catalysts, and analytical information regarding the product streams are preferably
15 stored in a database.

Where the multi-step synthesis involves performing different steps in different reactors, the steps involve obtaining a suitable reactor that includes a plurality of voids, placing an effective amount of a catalyst (or a catalyst combination) from one or more catalyst libraries in a void, repeating this step as necessary with different voids and different
20 catalysts so that a plurality of catalysts can be simultaneously evaluated, and performing the first step of the multi-step synthesis. The product streams can be and preferably are evaluated and optimized at this point. An optimized product stream can then be sent to a separate reactor and the second step of the multi-step synthesis performed in substantially the same manner as in the first step, albeit with different catalysts, reactants and reaction
25 conditions. This step is also optimized. The steps can be repeated as desired if the multi-step synthesis includes more than two steps.

The first step is preferably optimized using a lead generation approach to identify suitable catalysts and reaction conditions. These leads can be scaled up in a lead optimization step to identify the best conditions from a given set of leads. Once these
30 conditions are optimized and the ideal product stream is identified, this product stream can be used in the second step. This provides an advantage over conventional chemistry where a hypothetical reactant is used to approximate what would be used commercially. An

WO 02/07870

PCT/US01/22128

advantage of using the actual product stream from the previous step is that impurities that might affect the chemistry, but which would not be observed with a hypothetical reactant, are present in the actual product stream. This can provide more reliable results than when hypothetical reactants are used.

5 While it can be preferred to use the product stream directly from the optimized first step in a lead generation step, the product from the first step can alternatively be purified, for example via distillation, and the purified product used to evaluate the second step in the multi-step synthesis. The choice of whether to use the product from the first step directly in the second step is largely dependent on how the chemistry would be performed
10 commercially.

The product streams can be analyzed in a similar manner to how the product streams are analyzed in the embodiment where the plurality of steps in the multi-step synthesis are conducted in the same reactor.

The methods can advantageously be used to generate a database of catalysts and,
15 optionally, reaction conditions, which provide various product streams. As market conditions vary and/or product requirements change, conditions suitable for forming desired products can be identified with little or no downtime using the methods described herein.

While preferred embodiments of the present invention have been shown and described, it will be apparent to those skilled in the art that many changes and modifications
20 may be made without departing from the invention in its broader aspects. The appended claims are therefore intended to cover all such changes and modifications as fall within the true spirit and scope of the invention

WO 02/07870

PCT/US01/22128

We claim:

1. A method for discovering optimum catalyst systems and/or reaction conditions for multi-step synthetic reactions, comprising:
 - a. preparing a first library of catalysts for carrying out the first step of a desired multi-step reaction,
 - b. preparing a second library of catalysts for carrying out the second step of a desired multi-step reaction,
 - c. placing one or more catalysts from each library in a void in a reactor,
 - d. repeating step c until a desired number of catalysts have been placed in a desired number of voids, and
 - e. feeding reactants to the voids containing catalysts under conditions that cause the reactants to be converted to products.
2. The method of claim 1, further comprising analyzing the reaction products.
3. The method of claim 1, wherein at least one of the catalysts is a Fischer-Tropsch catalyst.
4. The method of claim 1, wherein at least one of the catalysts is a zeolite catalyst.
5. The method of claim 1, wherein at least one of the catalysts is a dehydrogenation/hydrogenation catalyst.
6. The method of claim 1, further comprising storing information regarding the identity of the catalysts and their position in the reactor.
7. The method of claim 2, further comprising storing information regarding the analysis of the reaction products in a database.
8. The method of claim 1, wherein the catalysts are arranged in the reactor in the form of a logical array.
9. The method of claim 1, wherein step e is repeated at least one time using different reaction conditions.
10. The process of claim 9, wherein the reaction conditions that are varied are selected from the group consisting of temperature, pressure, reactant composition, and flow rate.
11. The method of claim 1, wherein the product stream includes iso-paraffins in the jet fuel range.
12. The method of claim 1, wherein the product stream includes iso-paraffins in the diesel fuel range.

WO 02/07870

PCT/US01/22128

13. The method of claim 1, wherein the product stream includes iso-paraffins in the lube base oil range.
14. A method for discovering optimum catalyst systems and/or reaction conditions for multi-step synthetic reactions, comprising:
- 5 a. preparing a first library of catalysts for carrying out the first step of a desired multi-step reaction,
- b. preparing a second library of catalysts for carrying out the second step of a desired multi-step reaction,
- c. placing one or more catalysts from the first library in a void in a first reactor that
10 comprises a plurality of voids,
- d. repeating step c until a desired number of catalysts have been placed in a desired number of voids,
- e. feeding reactants to the voids containing catalysts under conditions that cause the reactants to be converted to products,
- 15 f. preparing a second reactor that comprises a plurality of voids by placing one or more catalysts from the second library in a void in the second reactor,
- g. repeating step f until a desired number of catalysts have been placed in a desired number of voids, and
- h. feeding at least a portion of the products from the first reaction, optionally
20 following a purification step, to the voids in the second reactor under conditions that cause the reactants to be converted to products.
15. The method of claim 14, further comprising analyzing the reaction products.
16. The method of claim 14, wherein at least one of the catalysts is a Fischer-Tropsch catalyst.
- 25 17. The method of claim 14, wherein at least one of the catalysts is a zeolite catalyst.
18. The method of claim 14, wherein at least one of the catalysts is a dehydrogenation/hydrogenation catalyst.
19. The method of claim 14, further comprising storing information regarding the identity of the catalysts and their position in the reactor.
- 30 20. The method of claim 15, further comprising storing information regarding the analysis of the reaction products in a database.

WO 02/07870

PCT/US01/22128

21. The method of claim 14, wherein the catalysts are arranged in the reactor in the form of a logical array.
22. The method of claim 14, wherein step e is repeated at least one time using different reaction conditions.
- 5 23. The process of claim 22, wherein the reaction conditions that are varied are selected from the group consisting of temperature, pressure, reactant composition, and flow rate.
24. The method of claim 14, wherein step h is repeated at least one time using different reaction conditions.
- 10 25. The process of claim 24, wherein the reaction conditions that are varied are selected from the group consisting of temperature, pressure, reactant composition, and flow rate
26. The method of claim 14, wherein the product stream includes iso-paraffins in the jet fuel range.
- 15 27. The method of claim 14, wherein the product stream includes iso-paraffins in the diesel fuel range.
28. The method of claim 14, wherein the product stream includes iso-paraffins in the lube base oil range.
29. A method for optimizing multi-step synthesis involving a single catalyst that
20 performs multiple steps, comprising:
 - a. preparing a catalyst library by taking a single catalyst and subjecting it to a plurality of additions or modifications to form a library of catalysts,
 - b. placing one or more catalysts from the library in a void in a reactor that comprises a plurality of voids,
 - 25 c. repeating step b until a desired number of catalysts have been placed in a desired number of voids, and
 - d. feeding reactants to the voids containing catalysts under conditions that cause the reactants to be converted to products.
30. The method of claim 29, further comprising storing information regarding the
30 identity of the catalysts and their position in the reactor in a database.
31. The method of claim 29, further comprising analyzing the reaction products.

WO 02/07870

PCT/US01/22128

32. The method of claim 31, further comprising storing information regarding the analysis of the reaction products in a database.
33. The method of claim 29, wherein the library comprises zeolite catalysts.
34. The method of claim 33, wherein the zeolites are modified by impregnating or
5 exchanging different metals or levels of metals in the zeolites.
35. The method of claim 29, wherein the catalysts are arranged in the reactor in the form of a logical array.
36. The method of claim 29, wherein step d) is repeated at least one time using different reaction conditions.
- 10 37. The process of claim 36, wherein the reaction conditions that are varied are selected from the group consisting of temperature, pressure, reactant composition, and flow rate.
38. The method of claim 29, wherein the product stream includes iso-paraffins in the jet fuel range.
- 15 39. The method of claim 29, wherein the product stream includes iso-paraffins in the diesel fuel range.
40. The method of claim 29, wherein the product stream includes iso-paraffins in the lube base oil range.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.